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ISOCAMPHOLACTONE

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I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY
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W. A. Noyes

In Charge of Thesis

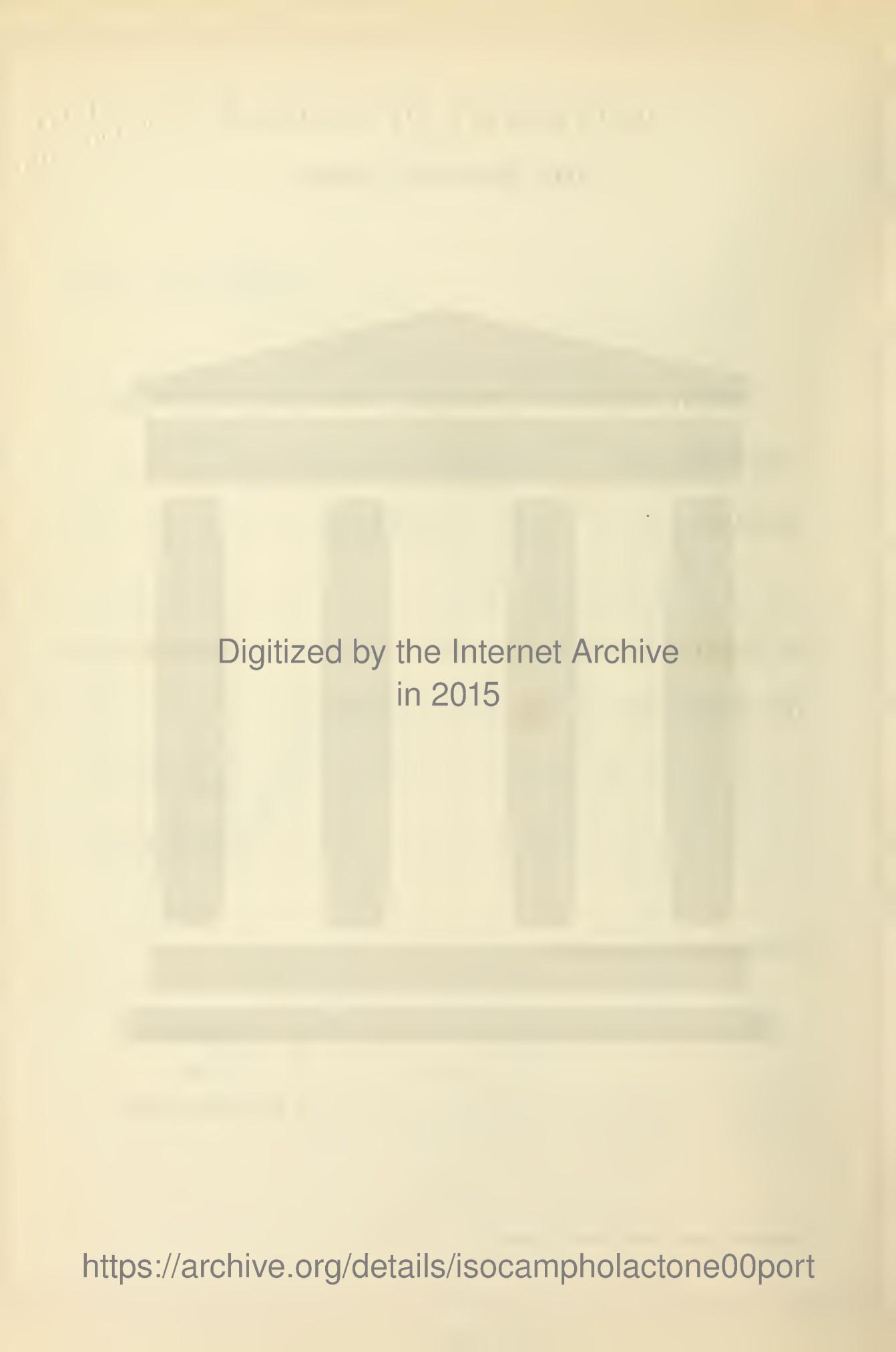
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Recommendation concurred in*

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on
Final Examination*

*Required for doctor's degree but not for master's

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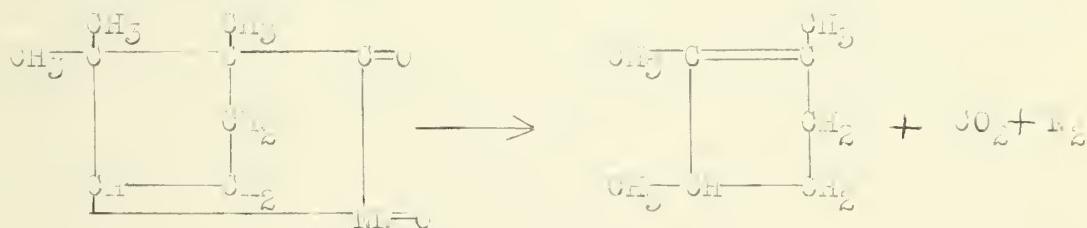
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ISOCYAN DERIVATIVES

I INTRODUCTION

Camphor and its derivatives often undergo molecular rearrangements. Very little is known concerning the laws and even a rearrangement, as it is often extremely difficult to determine whether a rearrangement has taken place in a given reaction or not. The first step in determining whether a rearrangement has taken place is to prove the structure of the compound resulting from this rearrangement. This is often difficult for one must use a sort of cumulative evidence, which is obtained from a study of the reactions and decomposition products of the compound.

The study of the derivatives of camphor give the examples of rearrangements. When the nitroso derivative of the amide of amino lauric acid is treated with sodium hydroxide, lauroleic is formed as one of the products.¹



In this reaction, the carbonyl and amino groups leave the molecule as carbon dioxide and nitrogen, and a methyl group shifts to form the 1,2,5-trimethyl compound.

In the same reaction, isocampholone is formed. As the structure of this compound has not been proven, there is a strong possibility that another type of rearrangement is taken place. The object of this work was to continue the study of the reactions

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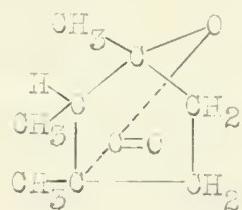
Noyes and Verick, J. Am. Chem. Soc. 31, -669

of isocamphorolstone, and impossible, to throw some light upon the possible structure of the compound, and nature of the rearrangement, if one has taken place. The work accomplished so far has made but very little progress toward the study of the larger question in view, and is quite incomplete. However, the series of reactions which lead to the preparation of isocamphorolstone have been studied, and in most cases, an increase in yields have been obtained by using either the methods that have been described, or by making certain modifications in the preparations.

LACTONES AND

Three lactones are known which correspond to some hydroxy acids that retain the tertiary carbonyl of camphoric acid. They are the campholactone, the cis-camphonololactone, and the iso-campholactone.

Campholactone was first prepared by Fitting and Loringer¹ by warming lauroolic acid with dilute mineral acid. It has been prepared by Noyes and Burke² by using this method. As laurolene has also been prepared by the distillation of lauroolic acid³, the shifting of the methyl group to form the 1,2,3, trimethyl compound may have occurred either during the formation of lauroolic acid or during its decomposition to form lauroene. The experimental work of Noyes and Burke² shows that the shift of the methyl group takes place in the formation of lauroolic acid. This gives the structure of campholactone as being formed by a rearrangement of the methyl groups giving the 1,2,3 trimethyl compound. Its structure may be represented by the following formula.



Cis-camphonololactone was first obtained by Noyes and Leveau⁴, who decomposed the nitroso derivative of the anhydride of amino lauric acid by warming it with a 10% solution of NaOH. Bredt⁵

¹ Fitting and Loringer, Ann. 227,-10

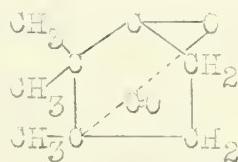
² Noyes and Burke, J.A.C.S. 54,-182

³ Walker and Henderson, J. Chem. Soc. 69,-749

⁴ Noyes and Leveau, Ann. Chem. J. 35,-385

⁵ Bredt, Ann. 361,-1

later prepared it by the electrolytic reduction of camphonic acid. The structure of camphononic acid has been shown by Lapworth and Lenton¹ to consist of no molecular rearrangement. By the reduction of camphononic acid, the cis-camphoric acid is formed, which upon heating gives the cis-camphololactone. This lactone has been oxidized back to the camphononic acid. This series of reactions show that cis-camphololactone is formed with no molecular rearrangement, and its structure may be represented by the following:



Iscampholactone is the third lactone known, which retains the tertiary carboxyl of camphoric acid. It was first obtained by the action of nitrous acid on amino lauronic acid. It was later prepared by Bredt² by decomposing the nitroso derivative of the anhydride of aminolauronic acid with sodium hydroxide. This method was repeated by Mojes and Faveau³ and by Mojes and Homberger⁴ who made a further study of the lactone.

The structure of this lactone has not been proven and it is still open to question. The possibility of a more complicated rearrangement in the formation of the lactone is entirely probable.

Iscampholactone has been oxidized by nitric acid, which formed as the principle product, the nitro-isocampholactone $\text{C}_8\text{H}_{15}(\text{NO}_2)\text{C}_6$ and also an acid $\text{C}_9\text{H}_{12}\text{O}_4$, melting at 138°C . The titration with standard alkali against 1 N acid gave results corresponding to the molecular weight of 166.0 and 166.9 for a monobasic

¹Lapworth and Lenton, J. Chem. Soc. 79,-1264

²Bredt, B. 35,-1901

³Mojes and Faveau, A.S.B. 32,-588; 33,-379; ⁴A.S.B. 31,-279; 32,1665

acid. That the acid contains a lactone group, was shown by heating a portion of it in a sealed tube with an excess of sodium hydroxide. .0508 grams of the acid neutralized 0.57 cc. of $n/10$ NaOH, the calculated amount for a dibasic acid being 0.18 cc. The barium salt and the amide were also prepared from the acid.

The nitro-iso-campholactone was reduced to the amino-iso-campholactone $C_8H_{13}(NH_2)CO$ and also the hydroxylaminoisocampholactone, $C_8H_{13}(NHOL)CO$.

Perhaps the most interesting reaction in the study of this compound, is the decomposition of the nitroisocampholactone by ammonium hydroxide, and sodium hydroxide to form compounds of six carbon atoms in the molecule while carbon dioxide is given off. Upon warming the nitro lactone with alcoholic ammonia or on treatment with cold concentrated aqueous ammonium hydroxide, the amide is formed, which has been given the following empirical formula, $C_8H_{13}NO_2$. This amide was saponified with .5N NaOH, giving an acid melting at 75°C .

Upon treating the nitroisocampholactone directly with .5N NaOH, carbon dioxide is given off, and upon acidifying, an acid was obtained, which was identical with the acid obtained from the amide. Titration of the acid with $n/10$ NaOH gave a molecular weight of 162.9 and 163, and titration with barium hydroxide gave 163. The theoretical molecular weight for $C_8H_{13}NO_2$ being 169.

A further study of these compounds may throw some light upon the possible structure of the lactone.

JOURNAL OF POLYMER SCIENCE

POLYMERIZATION OF CAMPHEMIC ACID.

Camphemic acid was polymerized according to the method described by Noyes¹, except that a fourth oxidation was made in the monomer liquor, which gave a desirably low yield, if not theoretical.

The yield of polymerizable materials varied from 54 to 60% theoretical, or an average of 59%. Larger quantities of camphemic acid were oxidized at a time, and the same results were obtained.

POLYMERIZATION OF CAMPHEMIC ANHYDRIDE.

Campheamic anhydride was prepared according to the method as described by Noyes¹. Larger quantities, as 500 grams of campheamic acid, were used at one time, and as good yields were obtained. The yields varied from 80 to 93% theoretical, with an average of 89%.

POLYMERIZATION OF ALPHA AND BETA CAMPHEMICIDIC ACIDS.

The alpha and beta campheamicidic acids were prepared according to the methods described by Noyes and Laveau². 50 grams of campheamic amine were treated with 80 cc. of concentrated ammonium hydroxide, and 15 cc. water in a pressure bottle. The bottle was wrapped in a towel, and shaken for ten minutes, after which it was placed in a cold water bath, and gradually heated, stirring it occasionally. A practically clear solution should be obtained. After cooling somewhat, the contents in the bottle were poured into a beaker, and cooled as rapidly as possible with constant stirring. The ammonium salt of the alpha acid crystallized out and was filtered.

¹ Noyes, J.A.S.J. 19,-501, 502

² Noyes and Laveau, J.A.S.J. 32,-283

ea off. It was purified by recrystallization from a small amount of warm water and ammonia.

The filtrate from the alpha salt contained the salt of the beta acid. To this, 30 cc. of sodium hydroxide (5 cc. = 1 gram.) were added, with stirring, and the sodium salt of the beta acid was precipitated. The filtrate from this solution, and the mother liquors from the purification of the alpha salt were carefully neutralized with hydrochloric acid. The solution was constantly stirred, and the acid added very slowly until the mixed acids began to separate out as a crystalline product. The addition of a small amount of some mixed acids from a previous preparation may prevent the precipitation of the acids, as a gummy product. The acids were filtered, and then dissolved in a little more than the theoretical amount of ammonium hydroxide and the separation repeated.

To obtain the free amidic acids, the ammonium or sodium salt was dissolved in water, and concentrated hydrochloric acid was added, using the same precautions, to insure a crystalline product being formed. The yields varied from 55 to 63% by weight of the alpha salt, and from 30 to 68% of the beta salt. Precipitation of the acids from the salts gave yields varying from 75-78% of the alpha acid, and from 50-55% of the beta acid. The yields of acids based upon the amount of camphoric anhydride used, gave from 45-50% by weight of the alpha acid, and from 35-45% of the beta acid.

Preparation of Amino Lauronic Acid.

Amino lauronic acid was prepared according to the method as described by Noyes¹. 199 grams (1 mole) of the alpha acid were

dissolved in a liter of a 10% solution of NaOH. 51 cc. or 100 g. of bromine were dissolved in 1400 cc. of a 10% solution of NaOH, and this solution of hypobromite added to the solution of the alpha acid. The solution was heated on a water bath to about 75° for 15 minutes. After cooling, a little sodium sulfite was added, and the solution was strongly acidified with HCl. The solution was then evaporated, and the amino acid separated out as the hydrochloride, and may be purified by a recrystallization from water. The yield was about 100% theoretical.

Preparation of the Anhydride and the Nitroso Derivative
of Amino Lauronic Acid.

The anhydride of amino lauronic acid has been prepared by the following methods; by distilling the hydrochloride of amino lauronic acid with an excess of lime¹; by heating the free amidic acid to 300° in an oil bath²; by heating the hydrochloride with acetic anhydride³; and, by heating the hydrochloride with acetic anhydride and fused sodium acetate⁴. From all of these methods, the nitroso derivative was obtained by dissolving the anhydride in dilute HCl and adding sodium nitrite.

All of these methods were tried, with varying yields of nitroso. However, it was thought best to write these two reaction, and not isolate the pure anhydride, which was done as far as possible.

Five and two tenths grams of the free acid were heated in a Wood's metal bath at 300° for one hour. The anhydride formed was dissolved in ether and the ether distilled off. The impure anhydride was then dissolved in dilute HCl, and sodium nitrite added.

¹

Noyes, J.A.C.S. 18,-507

²Noyes and Taveau, J.A.C.S. 32,-287

³Krebs, B. 55,-1291

⁴Noyes and Rutter, J.A.C.S. 37,-196

.638 grams of the nitroso derivative were obtained, or 12% by weight from the amount of amino lauronic acid taken.

Five and two tenths grams of the hydrochloride with 10 cc. of acetic anhydride and 2 grams of fused sodium acetate were heated 2 hours over a very small flame. The anhydride was obtained by extracting with ether. It was then dissolved in dilute HCl, and sodium nitrite added. 2.066 grams of the nitroso derivative were obtained, or 40% yield by weight.

Five and two tenths grams of the hydrochloride and 11 grams of lime were heated in a Wood's metal bath for one and one-half hours at a temperature of 280°. The mass was extracted twice with hot water, filtered, acidified with HCl, cooled, and sodium nitrite added. 2.226 grams of the nitroso derivative were obtained, or a yield of 43% by weight.

It was found however, that by distilling a mixture of the hydrochloride and calcium carbonate instead of lime, better yields than those from the ether method were obtained.

Twenty grams of the hydrochloride and 40 grams of calcium carbonate were mixed, and put into a retort. The mass was then heated quite strongly with a free flame. The anhydride formed, was distilled over into a flask cooled by ice water, or it sublimed in the neck of the retort. The heating was continued for about one-half hour, or until all of the anhydride had distilled, or sublimed. Upon cooling, the anhydride and the mass in the retort were extracted three times with hot water, and filtered, the anhydride being soluble in water. The filtrate was acidified with HCl and cooled. Sodium nitrite was added with constant stirring,

to insure the precipitation of the nitroso as a crystalline product. It was sometimes necessary to inoculate the solution with some previously prepared nitroso, to prevent the formation of a gummy and less pure compound. The nitroso derivative was purified by crystallizing once from alcohol. It melts at 156° - 159° .

The yields varied from 10.5 grams to one high yield of 15.8 g. which was an average yield of 11.5 grams or 66% theoretical from the amount of aniline lauric hydrochloride taken.

Preparation of Iso-campholactone.

Iso-campholactone was prepared by the method as described by Royes and Laveau¹ using a 10% solution of NaCl, and also by the method as described by Royes and Trotter² in their preparation of cis-camphorolactone, using a 30% solution of NaOH. The only modification made in their method was the fact that after distilling off the lauroline, the solution was made acid, and steam distilled directly without extracting the acids and lactones with ether. Due to the fact that the cis-camphorolactone could not be prepared, perhaps by the use of the stronger sodium hydroxide, and the higher temperature caused by the heat of reaction, and being somewhat volatile with steam, a mixture of the two lactones were obtained. These separated by refluxing the lactones with a 3% solution of NaOH for 30 minutes, which dissolved the cis-camphorolactone, and part of the isocampholactone. The solution was cooled to zero degrees and acidified, separating the isocampholactone as the hydrochloric acid corresponding to the cis-camphorolactone. These were ex-

¹ Royes and Laveau, J.A.C.S. 32,-286
Royes and Trotter, J.A.C.S. 34,-63

tracted with ether, and the ether distilled off under diminished pressure so as to keep the temperature low. The hydroxy acid was then dissolved in a potassium carbonate solution, and the isocampholactone was purified by distillation under diminished pressure.

The boiling point of the isocampholactone was $121^{\circ}-122^{\circ}$ at 25 mm. pressure, and the melting point was $50^{\circ}-52^{\circ}$. The yield was about 25% by weight from the amount of nitroso derivative taken.

Preparation of Nitro-isocampholactone.

Nitro-isocampholactone was prepared according to the method as described by Noyes and Sonnberger¹. 2.031 grams of the isocampholactone and 5 cc. of nitric acid (sp. gr. 1.47) were refluxed in a 50 cc. flask over a steam bath, until the oily layer of lactone disappeared, a little concentrated acid being added from time to time. Upon cooling and dilution with water, the nitro-isocampholactone crystallized out. 1.2 grams of the nitro lactone were obtained, melting at $121-122$, or a yield of 45% theoretical.

Preparation of Camphoric Imide.

Fifty grams of β -camphoramic acid and 100 cc. of concentrated HCl and 25 cc. of water were refluxed over a steam bath for 24 hours. The solution was then cooled and the imide filtered off. The impure imide was purified by dissolving it in 200 cc. of a 5% solution of NaOH, and reprecipitating it by passing a strong current of CO_2 through the solution. The yield was 25.7 grams of 72% theoretical. It melts at 245° .

The filtrate from the camphoric imide gave a precipitate of camphoric acid when acidified with HCl. An attempt was made to prepare the imide from ~~β~~-camphoramic acid by the same method.

however, no imide was obtained, but only camphoric acid was prepared. So, the amount of hydrolysis of both the α and β -camphoramic acids to camphoric acid was obtained by determining the amount of ammonium chloride obtained in the reaction.

1.0012 grams of α -camphoramic acid with 2 cc. of concentrated HCl, and .5 cc. of water were refluxed on a water bath for 24 hours. The solution was then slowly evaporated to dryness on a water bath, and the residue extracted with water to dissolve the ammonium chloride formed by the hydrolysis. The solution was diluted to 50 cc. from which two samples of 20 cc. each were pipetted off, and an excess of sodium carbonate added to each sample. Air was passed through the solution for three hours, drawing the ammonia into standard acid, and the excess acid titrated with standard alkali. The two samples were equivalent to 14.9 and 15.005 cc. of .0924 N acid respectively, or the total volume of 50 cc. of solution was equivalent to 37.38 cc. of acid. This being equivalent to .1878 grams of ammonium chloride shows that 38.64% of the acid is hydrolysed to camphoric acid.

Five grams of the β -camphoramic acid were treated in like manner as the α -acid. The two sample of 20cc. each were equivalent to 14.11 cc. and 14.28 cc. of .0924 N acid respectively, or the total volume of 50 cc. was equivalent to 35.5 cc. of acid. This being equivalent to .1775 grams of ammonium chloride, shows that 33.2% of the β -acid is hydrolysed. A second determination was made in the same manner, and 14.4% of β -acid was found to be hydrolysed.

Attempted preparation of α and β -Camphoramic
acids from Camphoric-imide.

Twenty five grams of the imide were dissolved in 80 cc. of

15% NaOH and the solution was heated on a water bath for one and one-half hours. On cooling and adding a crystal of some β -salt, the sodium salt separated and filtered off. The salt was dissolved in water, and the β -acid precipitated by HCl. The yield is about 14-15 grams of β -acid. The alkaline mother liquor was acidified with HCl, in hopes of obtaining some impure α -acid, but none was obtained. The possibility of a further hydrolysis to camphoric acid will be studied later.

ACKNOWLEDGMENT

The writer wishes to express his thanks to Doctor William A. Noyes for the many valuable suggestions in connection with this investigation.

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